# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
**United States Patent and Trademark Office**
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/344,189 | 06/24/1999 | CHARLES E. ROGLER | 0342/1D888US | 8764 |

7590 06/25/2003

DARBY & DARBY
ANNE E ZITRON PH D
805 THIRD AVENUE
NEW YORK, NY 10022

| EXAMINER |
|---|
| PARAS JR, PETER |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 28 |

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| ***Interview Summary*** | **Application No.** 09/344,189 | **Applicant(s)** ROGLER, CHARLES E. | |
|---|---|---|---|
| | **Examiner** Peter Paras, Jr. | **Art Unit** 1632 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *Peter Paras, Jr.*. (3)_____.

(2) *Mitch Bernstein*. (4)_____.

Date of Interview: *24 June 2003*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *see attached interview agenda and proposed claims*.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

PETER PARAS
PATENT EXAMINER

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: All the rejections of record were discussed. With regard to the enablement rejection Applicant's representative argued that it would not require undue experimentation to practice the invention as claimed because the specification teaches that hemizygous or homozygous uPA transgenic mice can be used. Since the claimed invention can be practiced with only two possible mice Applicant's representative asserted that it would not have required undue experimentation to practice the invention as claimed. .

DARBY &
DARBY
Professional
Corporation

805 Third Avenue
New York, NY 10022
Tel: (212) 527-7700
Fax: (212) 753-6237

INTELLECTUAL PROPERTY LAW

FILE #: 3368/1D888-US1

DATE: June 23, 2003

FROM: Mitchell Bernstein, Ph.D. E-MAIL: mbernstein@darbylaw.com

PHONE: (212) 527-7708

NO. OF PAGES: 11

| FACSIMILE NO. | RECIPIENT AND COMPANY | CONFIRMATION NO. |
|---|---|---|
| 703-746-5304 | Examiner Peter Paras, Jr.<br>USPTO, GAU 1632 | No |

COMMENTS:
Examiner Paras,
Further to our earlier conversation, I have attached form PTOL-413A and a set of draft claims. I will call you tommorow at 2:00 PM, as we agreed.

FYI: The form PTOL-413A you attempted to send was not part of the fax I received. I obtained the attached form directly from the USPTO web site.

–Mitch Bernstein

**PLEASE RETURN TO MITCHELL BERNSTEIN, PH.D.**

*** IF YOU DO NOT RECEIVE ALL PAGES, PLEASE TELEPHONE US IMMEDIATELY AT (212) 527-7774**



M:\3368\1d888\00016252.DOC

PTOL-413A (05-03)
Approved for use through xx/xx/xxxx. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

# Applicant Initiated Interview Request Form

Application No.: 09/344,189 First Named Applicant: Charles E. ROGLER
Examiner: Peter Paras, Jr. Art Unit: 1632 Status of Application: Non-final rej.

**Tentative Participants:**
(1) Examiner Paras (2) Mitchell Bernstein
(3) (4)

**Proposed Date of Interview:** 6/24/03 **Proposed Time:** 2:00 (AM/PM)

**Type of Interview Requested:**
(1) [X] Telephonic (2) [ ] Personal (3) [ ] Video Conference

**Exhibit To Be Shown or Demonstrated:** [X] YES [ ] NO
**If yes, provide brief description:** Draft claims

## Issues To Be Discussed

| Issues (Rej., Obj., etc) | Claims/ Fig. #s | Prior Art | Discussed | Agreed | Not Agreed |
|---|---|---|---|---|---|
| (1) Rej. | Cl. 1-48 | Mercer et al. | [ ] | [ ] | [ ] |
| (2) | | | [ ] | [ ] | [ ] |
| (3) | | | [ ] | [ ] | [ ] |
| (4) | | | [ ] | [ ] | [ ] |

[ ] Continuation Sheet Attached

**Brief Description of Arguments to be Presented:** Amended claims overcome alleged indefiniteness; specification enables full scope of claims; Genentech v Novo Nordisk does not support rejection for lack of enablement.

**An interview was conducted on the above-identified application on** _____.

**NOTE:**
**This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01).**
**This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible.**

Mitchell Bernstein
(Applicant/Applicant's Representative Signature) (Examiner/SPE Signature)

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

Claim 1 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; thereby making said chimeric mouse ~~transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus~~.

Claim 2 (Currently amended): The method of claim 1, ~~which~~ further comprising ~~comprises~~ infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

Claim 3 (Currently amended): The method of claim 1, ~~which~~ further comprising ~~comprises~~ infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

Claim 4 (Currently amended): The method of claim 1, ~~which comprises selecting~~ wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

Claim 5 (Original): The method of claim 1, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 6 (Original):

The method of claim 1, wherein the immunetolerant mouse which has a degenerated liver is created by:

a. crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2 (RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b. crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

Claim 7 (Original): The method of claim 6, wherein the xenogenic mammalian hepatocyte is from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 8 (Previously amended): A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, said degenerated liver being repopulated

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

with transplanted xenogenic mammalian hepatocytes that are infected with a compatible mammalian hepatitis virus.

Claim 9 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

Claim 10 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

Claim 11 (Original): The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes is a member selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Claim 12 (Original): The chimeric mouse model system of claim 8, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 13 (Currently amended): The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and is homozygous for ~~the~~ a Recombination Activation Gene 2 (RAG-2) knockout gene.

Claim 14 (Original): The chimeric mouse model system of claim 13, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 15 (Currently amended):

A method for screening a test compound for anti-viral activity, comprising:

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus; thereby screening said test compound for anti-viral activity.

Claim 16 (Original): The method of claim 15, wherein the mammalian virus is at least one hepatitis virus.

Claim 17 (Original): The method of claim 15, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

Claim 18 (Original): The method of claim 15, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus prior to said transplanting.

Claim 19 (Original): The method of claim 16, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus following said repopulating step.

Claims 20 (Original): The method of claim 15, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

Claim 21 (Original): The method of claim 15, wherein the compatible mammalian virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 22 (Currently amended): The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for ~~the~~ a Recombination Activation Gene 2 (RAG-2) knockout gene.

Claim 23 (Original): The method of claim 22, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 24 (Original): The method of claim 15, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

Claim 25 (Currently amended):

A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice that is repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

b. assaying said mice for the development of hepatocellular carcinoma virus; thereby screening said test compound for anti-cancer activity.

Claim 26 (Original): The method of claim 25, which comprises comparing the presence of unique viral DNA integrations in the liver of said mouse and in a control mouse which has not been administered the test compound.

Claim 27 (Original): The method of claim 25, wherein the chimeric mouse has precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue.

Claim 28 (Original): The method of claim 27, which comprises comparing the assay in the chimeric mouse with the same assay carried out in a control mouse which has not been administered the test compound.

Claim 29 (Original): The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with a hepatitis virus prior to said transplantation step.

Claim 30 (Original): The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting step.

Claim 31 (Original): The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulating step.

Claim 32 (Original): The method of claim 25, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

Claim 33 (Original): The method of claim 25, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

Claim 34 (Currently amended): The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for ~~the~~ a Recombination Activation Gene 2 (RAG-2) knockout gene.

Claim 35 (Original): The method of claim 33, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

Claim 36 (Original): The method of claim 25, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

Claim 37 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; thereby making said chimeric mouse.

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

Claim 38 (Currently amended): A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and

said degenerated liver ~~is~~ being repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

Claim 39 (Currently amended):

A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; and

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver; thereby making said chimeric mouse.

Claim 40 (Previously added): The method of claim 39 wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

Claim 41 (Previously added): The method of claim 40 wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

Docket No. 3368/1D888-US1
Serial No. 09/344,189

**Draft Claims (6.23.2003)**

Claim 42 (Previously added): The method of claim 1 wherein said uPA gene encodes secreted uPA.

Claim 43 (Previously added): The chimeric mouse model system of claim 8 wherein said uPA gene encodes secreted uPA.

Claim 44 (Previously added): The method of claim 15 wherein said uPA gene encodes secreted uPA.

Claim 45 (Previously added): The method of claim 25 wherein said uPA gene encodes secreted uPA.

Claim 46 (Previously added): The method of claim 37 wherein said uPA gene encodes secreted uPA.

Claim 47 (Previously added): The chimeric mouse model system of claim 38 wherein said uPA gene encodes secreted uPA.

Claim 48 (Previously added): The method of claim 39 wherein said uPA gene encodes secreted uPA.